REMARKS

Claims 11-17 are pending in the application. As a result of the modifications made herein, claim 11 is now cancelled and claims 12 - 17 have been amended. New matter has not been added to the specification or any claim.

DETAILED ACTION

OA Items 1-3. These Items summarize administrative matters.

CLAIM OBJECTIONS

OA Item 4. Claims 12-17 are rejected because they depend from cancelled Claim 1.

Claim 11 has been cancelled, Claim12 has been rewritten in independent claim form, and claims 13-17 have been amended to properly depend from Claim 12. Applicants believe that these amendments overcome this objection to claim dependency.

CLAIM REJECTIONS UNDER 35 USC 112

OA Items. 10, 10a, and 10b. Claims 11-17 are rejected as vague and indefinite for reciting the term mutein. Claims 12-17 are rejected as vague and indefinite for reciting the acronym N88R.

In response to the 35 USC 112 rejections identified above, claim 11 has been cancelled and claims 12 - 17 have been amended. Amendments in Claims 12 and 17 provide a specific description of the claimed mutein that identifies the invention with greater

particularity. These amendments are consistent with the description of one aspect of the invention presented on page 5 of the specification, in the first paragraph under the heading "Specific Embodiments". Applicants believe that these amendments overcome the § 112 rejections mentioned above.

CLAIM REJECTIONS UNDER 35 USC 103(a)

OA Item 11. Claims 11-17 are rejected under 35 USC 103(a) as being unpatentable over Andya et al (US Patent No: 6,267,958) in view of Shanafelt et al (WO 996018A1).

The OA says that Andya et al describe a stable lyophilized protein pharmaceutical formulation that can be reconstituted with a suitable diluent to generate a high protein concentration reconstituted formulation. Components of the formulation are listed. The OA notes that the reference does not explicitly recite a pharmaceutical composition comprising hIL-2 mutein stabilized with amino acids and sucrose.

The OA says that Shanafelt et al. discloses both IL-2 and the N88R variant of IL-2 in pharmaceutical compositions for therapeutic uses.

The OA concludes that it would therefore have been obvious to stabilize the interleukins disclosed in Shanafelt et al. using the amino acids and sucrose described in Andya in the claimed concentration ranges to produce stabilized interleukins for pharmaceutical formulations. The OA supports this conclusion by observing that Andya teaches that stabilized proteins including interleukins can be lyophilized and then reconstituted with little loss in activity.

APPLICANT'S REMARKS:

Applicants have amended Claims 12-17. Each of these claims is now directed to the stabilization of low concentration proteins, these low concentrations being very different

from the Andya stabilized proteins. The Andya patent teaches (in each of the Examples) the stabilization of two monoclonal antibodies at high concentrations (between 20 - 25 mg/ml), whereas applicants claim the stabilization a mutant cytokine at low concentration (1.0 to 4.0 mg/ml, and 0.1 to 4 mg/ml respectively). Moreover, Andya makes no statement that his technology is applicable to the stabilization of low concentration proteins. The distinction between the stabilization of high concentration proteins versus low concentration proteins is discussed below.

To establish a prima facie case of obviousness under 35 USC 103(a), three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when +combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, USPQ2d 1438 (Fed. Cir. 1991). The Federal Circuit has repeatedly noted: "it is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that 'one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988); see also *In re Gorman*, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

Applicants respectfully submit that one skilled in the art would not have arrived at Applicants' claimed invention based on the teaching of Andya and Shanafelt and the state of the art. The attention of the Office is directed to the guidance of MPEP Section 2164.03, which addresses the relationship of predictability in the art and the enablement requirement. In this section of the MPEP, instruction (referencing: In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA) 1970) is provided that *the amount of guidance or direction needed to enable an invention is inversely related to the amount of knowledge*

in the state of the art as well as the predictability in the art. And, *the predictability (or lack thereof) in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. ...* ***If one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is lack of predictability in the art.***

Applicants now respectfully direct the attention of the Office to the journal article of Dr. Wei Wang (Wang, International Journal of Pharmaceutics 203 (2000) provided in a Supplemental IDS with this Paper Number 17 response). **Dr. Wang reports on page 10 that "Not all proteins can be stabilized by sugars/polyols. This is an unsolved puzzle."** On page 12, Dr. Wang further discusses the problems associated with protein stabilization, he says, "***proteins at higher concentrations are often more resistant against both freezing and lyophilization induced protein denaturation/aggregation. The activity recovery of many labile proteins after freeze thawing correlates directly with initial protein concentration (Allison et al. 1996).***" And further on the same page ***"The mechanisms of protein self-stabilization during freezing and/or lyophilization have not been clearly delineated. Proteins are polymers, and therefore, at least some of the above discussed stabilization mechanisms for polymers may be applicable to protein self-stabilization. ...***" Dr. Wang's statements address the variations in protein stabilization that are dependent on the initial concentration of a protein being lyophilized. In general, high concentrations of proteins are inherently more stable than low concentrations. In the comments referenced above, and throughout the article, Dr. Wang is stating that the stabilization of high concentration proteins is not necessarily predictive of low concentration stabilization.

For each of the reasons presented above, applicants assert that a skilled practitioner would not have relied upon the teachings of Andya to obtain guidance applicable to the low concentration stabilization of the proteins disclosed by Shanafelt. As discussed by Dr. Wang above, protein stabilization is too unpredictable to conclude that the stabilization techniques employed by Andya would necessarily be applicable to any of the proteins listed in his patent or at any protein concentration. Please note that Dr.

Andya does not state that his stabilization technology was effective at concentrations below 20 mg/ml; **he is silent on that point**.

The Office is also respectfully reminded that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination and **there must be a suggestion or motivation in the reference to do so**. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990); (MPEP §2143.01).

The Andya patent provides enablement for the stabilization of only two human monoclonal antibodies (huMAb 4D5-8 [described in Example 1], and huMAb E25 [described in Example 2]). Despite the limited disclosure, the Andya specification speculates on an exceedingly large number other materials that may benefit from the stabilizing mixture, without regard to the concentration of the protein. There is no basis in the Andya patent for a skilled practitioner to conclude that the technology would necessarily be applicable to the extensive materials list. When one considers that Andya includes in his "list of proteins covered by the definition," an undefined collection of variants, it is impossible to reasonably conclude that the list could utilize the same stabilization formulation. The number and variety of protein compounds that would be included by this assertion is truly astronomical. By listing all the referenced molecules and their variants, what Andya has done is to list a gigantic number of proteins having extreme diversity in size, shape, and functionality (if any), and to suggest that they would be stabilized just like the two antibodies that Andya actually studied. In light of the limited enablement provided in the specification, the Andya statement regarding alternate protein stabilization is too broad for a scientist to rely on for guidance. (If requested by the Patent Office, a declaration attesting to this fact will be provided.)

For the reasons provided above, especially: the lack of predictability in protein stabilization (discussed by Dr. Wang); the extremely limited amount of enablement provided in the Andya patent; the fact that no enablement is provided in the Andya patent for the stabilization of any protein at concentrations comparable to the IL-2 muteins

claimed by applicants; and the guidance provided in MPEP section 2164.03 and by the various courts referenced above; applicants assert that the teaching of Andya and Shanafelt cannot be properly combined to render the presently claimed invention obvious.

In light of the arguments presented above, Applicants respectfully request that the Examiner reconsider this rejection of Claims 12-17 under 35 USC 103 and withdraw the rejection.

In conclusion, applicants believe that Claims 12-17 are now in condition for allowance, and each of the grounds of objection and rejection has been overcome, and prompt issuance of the present case is earnestly solicited.

A completed form PTO/SB/22 Petition for Extension of Time under 37 C.F.R. 1.136(a) to extend the period for filing a response by two months is herewith submitted.

A completed Supplemental Information Disclosure Statement, along with the associated journal article is also provided herewith.

The Patent Office is hereby authorized to charge Applicants' deposit account (Account number 03-4000) for any fees associated with the filing of this response, the Petition for an Extension of time to respond, and the Supplemental Information Disclosure Statement.

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call their Attorney at the phone number listed below.

Respectfully Submitted,

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